On Cancer Risk Estimation of Urban Air Pollution

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The usefulness of data from various sources for a cancer risk estimation of urban air pollution is discussed. Considering the irreversibility of initiations, a multiplicative model is preferred for solid tumors. As has been concluded for exposure to ionizing radiation, the multiplicative model, in comparison with the additive model, predicts a relatively larger number of cases at high ages, with enhanced underestimation of risks by short follow-up times in disease-epidemiological studies. For related reasons, the extrapolation of risk from animal tests on the basis of daily absorbed dose per kilogram body weight or per square meter surface area without considering differences in life span may lead to an underestimation, and agreements with epidemiologically determined values may be fortuitous. Considering these possibilities, the most likely lifetime risks of cancer death at the average exposure levels in Sweden were estimated for certain pollution fractions or indicator compounds in urban air. The risks amount to approximately 50 deaths per 100,000 for inhaled particulate organic material (POM), with a contribution from ingested POM about three times larger, and alkenes, and butadiene cause 20 deaths, respectively, per 100,000 individuals. Also, benzene and formaldehyde are expected to be associated with considerable risk increments. Comparative potency methods were applied for POM and alkenes. Due to incompleteness of the list of compounds considered and the uncertainties of the above estimates, the total risk calculation from urban air has not been attempted here. — Environ Health Perspect 102(Suppl 4):173–181 (1994).

Key words: air pollution, cancer risk, genotoxic potency, initiation, motor exhausts, multipliative model, promotion, target dose

Introduction

The main purpose of this paper is the estimation of cancer risks from urban air pollutants on the basis of data from carcinogenicity tests with laboratory animals. This paper serves as a parallel of the estimations based on epidemiological data presented by Hemminki and Pershagen (1). Both papers use the population-weighted exposure data for Sweden (Table 1), presented by Boström et al. (2).

Since any meaningful effort to arrive at reliable cancer risk estimates requires a multiprong approach (3–5), it is necessary to refer to complementary information from sources other than the long-term animal tests. For instance, epidemiological data may serve to check the reasonableness of risks estimated by extrapolation from animal carcinogenicity tests, even if they are unable to show a significant effect (3–5). This paper may be seen as a discussion of the usefulness for risk estimation of information from different sources.

Multiplicative versus Additive Models

In similarity with cancer risks from ionizing radiations, risks of chemically induced cancers have been expressed as a relationship between exposure dose or absorbed dose and individual risk (the probability of acquiring cancer) or collective risk (the expected number of cases in an exposed population) (6,7). Continued and extended follow-up of exposed populations, particularly atomic bomb survivors in Hiroshima and Nagasaki and groups with medical radiation treatment, revealed that radiation-induced incremental incidences are approximately proportional to background incidences:

$$P(D) = (1 + \beta D) \times P° \qquad [1]$$

where β is the risk coefficient for the linear dependence on the dose (D) assumed to prevail at low doses and $P°$ is the background

incidence. Earlier it was assumed that the risk has a dose-related absolute value:

$$P(D) = P° + kD \qquad [2]$$

where k is the risk coefficient.

To the extent that initiations are irreversible, a multiplicative increase of cancer incidence would be expected to result from exposure to initiators in general. The validity of a multiplicative model for chemicals is supported by the outcome of an evaluation of data from carcinogenicity tests of ethylene oxide (8). This model also has been applied to diesel exhausts (9,10) in the past. [It should be stressed that a linear multiplicative model is expected to hold at doses so low that the reversible cocarcinogenic and promotive effects do not occur (11).]

The validity of the multiplicative model agrees with results of experimental studies of radiogenic cancer where an additive model could be rejected in most cases in favor of the multiplicative model (12). For

Table 1. Average exposure to several airborne genotoxic substances in Sweden (2) and unit lifetime risk factors (15).

Substance	Mean annual exposure per m³	Unit risk factor per µg/m³
Polycyclic aromatic hydrocarbons	19.0 ng	1×10^{-1} (as B[a]P)
Benzo[a]pyrene	0.7 ng	—
Benzene	3.7 µg	8×10^{-6}
Formaldehyde	1.2 µg	1×10^{-5}
Acetaldehyde	1.0 µg	2×10^{-6}
Ethene	1.8 µg	1×10^{-4} (ethylene oxide)
Propene	2.3 µg	—
Butadiene	0.7 µg	3×10^{-4}

these reasons, the National Research Council (*13*) has adopted the multiplicative model. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) compares the two models (*14*). In this respect the leukemias present an exception. Probably due to depletion of the stem cells that existed at the time of radiation exposure, the raised incidence ceases after approximately 30 years. The shift to the multiplicative model led to a large number of cancer cases because an exposure earlier in life is expected to occur at those higher ages, around and above 65 years, where the background incidence undergoes a rapid rise. This also means that the total number of cases per unit of radiation dose will be some 4 times higher than was expected from the additive model. A small part of this increase is due to reevaluation of the atomic bomb radiation doses in Hiroshima and Nagasaki (*13,14*).

One consequence of the adoption of a multiplicative risk model will be that a considerable part of the risk, or number of cases in a population, is expected to occur towards the end of the life and will become a question of the manner of death rather than of years lost. In the past we have calculated risks from defined exposure doses in terms of probability per year, or number of cases per year, while considering a steady-state condition established if the exposure continues through decades. Due to the skew distribution of risk over ages, this way of expressing the risk may be misleading. Since exposure levels change fast—hopefully to the better—within times which are short in comparison to a human life span (70 years), it is important to stress that the risk from one year's exposure means the (average) probability, due to this exposure, of acquiring cancer at some time later in life. The annual risks calculated below from the unit lifetime risk coefficients of the EPA (Table 1) (*15*) for the risk from life-long exposure to 1 μg/m³ should be seen in this sense.

Methods for Risk Estimation

Epidemiology

Disease-epidemiological studies have a major drawback in their insensitivity (low power). A considerable increase of the incidence or death rate is required to show, with statistical significance, that there is an effect and an even higher increase is necessary to estimate the magnitude of the effect. Therefore, epidemiological studies are applied best in situations with a considerably raised exposure, as in work environments. The risks at lower exposure levels then can be estimated by

extrapolation. Other problems encountered are the long latency times, several years (for leukemias) to several decades, difficulties of reconstructing reliable exposure data, and the occurrence of confounding factors (e.g., differences in smoking habits and other lifestyle factors between exposed and control groups). Because of such difficulties, disease-epidemiological methods are of limited usefulness in risk assessment, particularly with regard to quantitative aspects.

The measurement of biological and chemical biomarkers permits a considerable increase of the sensitivity of epidemiological investigations, provided the relationship between observed biomarker level and risk can be established. The disadvantage of long latency can also be eliminated. Furthermore, the measurement of adducts from carcinogens (i.e. products of reaction with cellular macromolecules), a method that is several orders of magnitude more sensitive than disease-epidemiological investigations, permits identification of causative factors and thus avoids the influence of confounding processes of other factors.

Animal Carcinogenicity

Animal carcinogenicity tests are informative where human data are not available and are advantageous because administered doses are well defined and no confounding factors need to be considered in comparisons with control groups. However, problems are encountered, in the translation of observed excess incidences to human risks at low exposure levels. In this translation, two extrapolations are involved from animal species to man and from the usually high experimental doses (and dose rates) to the low ones in human target populations.

Animal carcinogenicity tests have the following problems. *a*) The high dose and dose rates that have to be applied in order to obtain decisive data from animal groups of limited size lead to side effects that could be described as cocarcinogenic or promotive, with consequential nonlinear dose-response relationships. Although this is accounted for to some extent by estimating the slope of the linear low-dose component of a multihit model (*16*), the reliability of the procedure should not be taken for granted. *b*) Interspecies differences in metabolism have been corrected for by scaling of the dose in mg/kg body weight to mg/m² body surface area, which decreases the overall metabolic rate with increasing body size (*16*). This procedure appears to be an administratively useful rule of thumb rather than an effort to find the true risk. *c*) The question whether the life-time dose or the dose per day (i.e., a

dose rate) determines the risk creates an uncertainty by a factor 35 corresponding to the human-to-rodent longevity ratio (*17*). Due to the irreversibility of genotoxic events, the lifetime dose is expected to have a decisive influence, as has been found for ionizing radiation (*12*) and recently for alkylating chemotherapeutics (*18*). Therefore, the extrapolation on the basis of daily dose, as done by the U.S. EPA (*16*), may lead to considerable underestimation. Partly, this underestimation is counteracted by scaling to the dose per unit body area, which renders humans about six times more sensitive than rats and about 13 times more than mice. Agreements found between risks estimated in this way from animal data and incidences observed in epidemiological studies (*19*) may be referred to as an underestimation of the latter in several cases due to follow-up times that were too short (*20*).

For instance, in the case of ethylene oxide, the human data are predominated by leukemias (i.e., the malignancies that appear with the shortest latency times) (*21*). The cohorts with exposure to ethylene oxide thus show a resemblance to the atomic bomb survivors in Hiroshima and Nagasaki who exhibited mainly leukemias in approximately the first 15 years (*7,8*). Due to the distribution of the dose to all tissues, ethylene oxide is expected to increase the incidence of solid tumors, which corresponds with observations in rats and mice in which ethylene oxide has been shown to raise the incidence of tumors of most types that occur normally in the animal strain (*8*). For carcinogens acting as promoters or cocarcinogens in nonlinear dose dependence, the situation will be more complicated mainly because the animal tests do not mimic the human situation with variable dose rate (concentration). It seems that determination of target doses in exposed humans and in laboratory organisms is a necessary step to solve these problems.

Comparative Potency Methods for Risk Estimation

If the risk coefficients (β_i or k_i in Equations 1 and 2) for a particular exposure i are unknown, these coefficients could be evaluated, at least in principle, through their relative potency in comparison with an agent j with known risk coefficients β_j or k_j, respectively. If we denote the relative potency by Q_{ij}

$$Q_{ij} = \frac{\beta_i}{\beta_j} = \frac{k_i}{k_j} \qquad [3]$$

Table 2. A few components of automotive engine exhausts, emitted per km (29).

		Gasoline exhausts		Diesel exhausts	
		Without catalyst	With catalyst	Light	Heavy
Gas phase					
Benzene	mg	100	8	15	ND
Formaldehyde	mg	35	2.5	12	ND
Fluoranthene	µg	280	4.4	186	770
Particle phase					
Particles	mg	62	110	245	1030
Benzo[a]pyrene	µg	12	0.25	8	34
Fluoranthene	µg	211	3.1	139	580
1-Nitropyrene	µg	0.2	<0.1	6.8	28
(B[a]P per mg particles)		(0.2)	(0.02)	(0.03)	(0.04)
Ratio of fluoranthene					
(total)/B[a]P		40	30	40	40

ND, no data.

the risks according to Equations 1 and 2 could be estimated through

$$P(D) = (1 + Q_{ij} \times \beta_j \times D_i)P° \quad [4]$$

or

$$P(D) = P° + Q_{ij} \times k_j \times D_i \quad [5]$$

for the relative and absolute risks, respectively. The values of Q_{ij} are determined by relevant bioassays. The approach is based on the assumption that the values of Q_{ij} are the same in the bioassay systems and in humans. Evidently the method is applicable at exposure levels that are low enough to make the dose-response relationships seem linear.

Two approaches have been forwarded to estimate cancer risks by comparative potency methods. Lewtas et al. (22,23) applied the principle for risk estimation of particulate organic matter (POM) from automotive engine exhausts and from other combustion processes, using the epidemiologically established coefficients for lung cancer risk in coke oven topside work as reference standard. The bioassay systems they used comprised a data base of several tests including tumor initiation by painting mouse skin with the methylene chloride (CH_2Cl_2) extracts to be compared. The method was validated by agreement between estimated and epidemiologically determined lung cancer risks from roofing tar emissions and tobacco smoking (23).

The Stockholm approach (20,24–26), often referred to as the rad-equivalence approach, initially was directed towards risk estimation of specific chemicals with low linear energy transfer (LET) radiation as reference standard. In this prospective risk model, the value of Q_{ij} is based on the target doses of the chemicals (i) determined by hemoglobin and/or DNA adducts and doses of γ radiation (j), prompting the same response.

Risk Estimation

PAH, POM, and Particles

The population-weighted average concentration of polycyclic aromatic hydrocarbons (PAH) in Sweden is given as 0.7 ng/m³ benzo[a]pyrene (B[a]P) (Table 1). With the EPA unit risk factor for lung cancer death from PAH this would correspond to an average risk of 7×10^{-5} from life-long exposure or eight cases of disease per year in the Swedish population of 8.4 million.

Under the Swedish Urban Air Project, PAH in the particulate fraction was estimated to cause approximately 65 cancer cases annually in Sweden (27). The estimate was based on a preliminary determination of the rad-equivalence of B[a]P in the mouse (7 rad-equivalence [mg/kg bw]$^{-1}$) (28) and an estimate of the average contribution of B[a]P (approximately 2%) to the response to total particle extracts (unpublished data). Judging the average level of B[a]P to be 0.5 ng/m³ and inhalation to be 20 m³/day, the cancer risk from B[a]P was estimated at 1.3 cases/year and the risk from ΣPAH to 50 × 1.3 = 65 cases/year (27). For the 0.7 ng/m³ now presented as a probable average level (Table 1), the corresponding number due to ΣPAH would be 90 cases annually in Sweden, corresponding to a lifetime risk of 80 × 10^{-5}. Since this value is not restricted to lung cancer but encompasses the total cancer incidence, the two figures are compatible. This does not mean, however, that the estimates are correct, even to the order of magnitude. The use of the unit risk coefficient for one component, B[a]P, is no doubt an oversimplification because many factors influencing risk are disregarded. These circumstances will be discussed briefly in the following section.

Relevance of Benzo[a]pyrene as PAH Indicator

Apart from the instability of B[a]P, several objections have been raised against the use of this compound as an indicator of the genotoxicity of PAH in air pollution. Part of the PAH is bound to particles, and PAH with 3 to 4 rings that are present largely in the gas phase are not included when the PAH analysis is carried out on extractable organic matter. Certain volatile or semivolatile PAH (e.g., methylphenanthrenes and fluoranthene) occur at relatively high concentrations (Table 2) and are effective mutagens (30). It has also been pointed out that although B[a]P may be a useful indicator of the carcinogenic potential of the PAH-rich coke oven emissions and similar emissions, its use for diesel-engine exhausts and tobacco smoke would represent only the PAH component of these emissions, which contain a broader range of carcinogenic components (31). Pott and Heinrich (32) have demonstrated by a compilation of epidemiological and experimental data that at equal lung cancer incidence provoked by fumes from heated pitch (as a model for coke oven emission), tobacco smoke, and diesel exhausts, the relative intakes of B[a]P are 1, approximately 0.01 and approximately 0.001, respectively.

It may appear that these differences are allowed for in the risk assessments of Lewtas (23) by the comparative potency method (see above). Expressing the lung cancer risk per µg/m³ of extractable organic material from diesel and gasoline exhaust particles, respectively, she arrives at risk coefficients of 2.3×10^{-4} and 1.2×10^{-4} with a weighted mean of about 2×10^{-4}. With an assumed average particle level of 5 µg/m³ in Sweden (Table 3), of which about 7% (33) is extractable, the associated risk would be

$$5(\mu g/m^3) \times \frac{7}{100} \times [2 \times 10^{-4} (\mu g/m^3)^{-1}]$$

$$= 7 \times 10^{-5} \quad [6]$$

Considering the rough approximations made, the value is compatible with the one based directly on the B[a]P content. This agreement may be fortuitous.

Table 3. Particle levels in polluted air in Sweden. [a]

	Diesel particles, µg/m³	Soot, µg/m³
Average in the country	1.0	3.7
Loaded city areas	1–2	8–10
High-traffic areas	2–4	

[a] C-E. Boström, personal communication.

Table 4. Estimated cancer risks from components in urban air pollution.

| | Unit risk estimate | Adopted estimate | |
	Individual lifetime risk of cancer death, $\times 10^5$	Individual lifetime risk of cancer death, $^a \times 10^5$	Cases of disease per year in Sweden ^{a}
Particle phase			
PAH, POM (as B[a]P)		50	100
Unit risk, lung cancer	7		
Diesel particles, lung cancer (41)	7		
Other particles	?		
Rad-equivalence, all cancer	(80)		
(diesel epidemiology, lung cancer)	(~100?)		
PAH uptake via food chain			~300
Gas phase			
PAH	?		?
Ethene, all cancer	1.4		
rad-equivalence, all cancer		13	30
Propene		2.1	5
Butadiene	21	21	~50
Benzene, leukemia	3		~5
All cancer			10
Other alkenes		?	?
Formaldehyde, nasal	1.2		
All cancer			25
Acetaldehyde	0.2		<1
Other carbonyls		?	?

Abbreviations: B[a]P, benzo[a]pyrene; PAH, polycyclic aromatic hydrocarbons; POM, polycyclic organic matter.
^{a} Considering theoretical and statistical errors, the figures given are judged to uncertain by a factor of three.

In the past several studies have demonstrated that the carcinogenic potency of B[a]P (and other PAH) is enhanced by adsorption to particles (34). The mechanism of this effect has remained obscure and is very complex. Apart from a carcinogenic action of the particles per se (see below), adsorption onto particles has been shown to increase the retention time in lung tissue of PAH such as B[a]P, partly by decreasing the rate of metabolism (35). This depot effect may lead to increased induction of PAH-metabolizing enzymes, as shown with respect to the formation of B[a]P 7,8- and 9,10-dihydrodiols in experiments with perfused lung (35,36) and raised levels of DNA-adducts of B[a]P metabolites, particularly the mutagenic 7,8-diol-9,10-epoxide, provided the desorption is not too slow (37). These enzyme inductions result in raised doses of genotoxic factors and may be seen as cocarcinogenic effects of an interaction with the Ah receptor. A number of facts further indicate that the promoter action of carcinogenic PAHs, which is also correlated with the receptor affinity (38), is exerted by the unmetabolized hydrocarbons rather than by genotoxic metabolites (39). The prolonged retention in lung tissue due to adsorption onto particles therefore may be seen as an increase of the promoter dose. Because a soot core with such adsorbing properties is not at hand in coke oven emission to what extent these effects can be

allowed for in risk estimation by the comparative potency method with lung cancer incidence in coke oven workers as reference standard has to be clarified (22,23).

A role of the particulate material in the development of lung tumors has been suspected (40), and Pott et al. (41) have demonstrated that the particles such as soot play a predominant role in the development of lung cancer in rats exposed to diesel exhausts. This finding is supported by the demonstration that PAH-free particles of various kinds (carbon black, quartz, titanium dioxide, etc.) are effective inducers of lung cancer in the rat (41,42). The organic material adsorbed on the particles is judged to contribute by no more than 1% to the effect.

Applying the multihit model of EPA (17) to the experimental data for lung cancer in rats caused by diesel exhaust exposure, Pott arrives at a lifetime risk of 7×10^{-5} per $\mu g/m^3$ particles (41). Because the average, airborne, diesel particle content in Sweden amounts to about 1 $\mu g/m^3$ (Table 3), the risk of 7×10^{-5}, or about eight cases per year in Sweden should be added to the value estimated from the B[a]P content in the air, which concerns mainly B[a]P from other sources, particularly gasoline exhausts (Table 4).

It is satisfactory, as a basis for preventive measures, that the carcinogenic action of particles has been demonstrated according to the above information and that a risk estimate has been provided for this factor. A number

of circumstances, however, render the numerical value of the estimated risk very uncertain. Too little is known about the mechanism of action to permit the prediction of a linear component in the dose-response curve; linearity in the low-dose region would be expected if single particles induce the production of free radicals that interact with DNA in target cells. It is indicated by the considerable size of the lungs after prolonged exposure (43,44) and the increased number of neutrophils in bronchoalveolar lavage fluid (40) that the particle burden provokes an inflammation that might act as a cancer promoter. Since the dose-response relationship of a nongenotoxic promoter action may have a no-effect threshold (11), the possibility that the risk is close to zero is not excluded, as also the risk is close to zero is not excluded, as also pointed out by Pott as well (41). It is also expected that the gaseous components to which the animals were simultaneously exposed play a minor role; this was shown for the epoxide doses from alkenes (45).

It is important to characterize the induction status of humans with respect to metabolism of PAH. It has been proposed that urban air may be polluted sufficiently to induce PAH metabolism (46), a putative mechanism of synergisms with xenobiotics from other sources. The risk estimate appears to be low, however, as compared to indications from epidemiological studies (which, it should be stressed, are also unable to exclude a threshold) (1). Consider, for example, the studies of Garshick et al. (47,48) of American railroad workers, the most extensive diesel-epidemiological study ever carried out. Disregarding that smoking data are incomplete, this study generates, according to evaluations of McClellan et al. (10) based on the most likely exposure level, 125 $\mu g/m^3$ particles (49,50) and at 500 $\mu g/m^3$, a higher but possible level, the lifetime risk figures are 120×10^{-5} and 30×10^{-5} per $\mu g/m^3$, respectively, corresponding to 150 or 40 lung cancer cases annually, respectively. These figures are about 10 times higher than those extrapolated from animal data (Table 4). If dose-response curves are linear in the low-dose range and if life-time doses are considered in the extrapolation, higher risk values would be obtained.

It should be realized that in studies limited to the particles or extracts from particles, contributions from volatile and semivolatile components are not recognized. As mentioned above, Barfknecht et al. (30) showed that fluoranthene, a quantitatively major component occurring in concentrations much higher than that of B[a]P, is an effective mutagen and contributes to 30%

of the mutagenicity in human cells of PAH from diesel particles. In contrast to B[a]P, the more volatile fluoranthene occurs partly in the gas phase (Table 2). Despite its high mutagenic effectiveness, confirmed by Vaca et al. (39), the carcinogenic potency of fluoranthene tested alone is about 100 times lower than that of B[a]P (51), except when administered together with B[a]P (52). For the proper risk estimation of ambient PAH, it appears that a key problem is clarifying the relevance of experiments with mice to risk in man, particularly by measurement of target doses through levels of macromolecule adducts.

Other Sites; Uptake via the Food

The previously mentioned preliminary risk estimate, where B[a]P was used as indicator led to approximately 65 cases per year in Sweden from particle-bound organic material (27). From a study of the origin of PAH in food (53), it was judged that not more than about 1/5 could be formed during food preparation such as grilling and that the remaining 4/5 might originate from precipitated particulate material. The dose from this intake was estimated to be five times larger than the dose received through inhalation. The collective risk in Sweden from this source was given as 300 cases per year (Table 4) (27). In other studies it has been confirmed that the dietary intake of PAH is large compared to the uptake via inhalation (54,55). However, the data for the uptake of PAH (or POM) via the food chain and for the origin of this material are limited.

Basic data for the dose distribution in the body following uptake of PAH or individual indicators via the respiratory tract and/or the gastrointestinal tract are still very incomplete. In epidemiological studies, exposure to motor exhausts has been associated with a raised incidence of tumors other than lung cancer, mainly bladder cancer (possibly with nitroarenes in diesel exhausts as a causative factor) and multiple myeloma (56). Chimney sweeps exhibit a raised incidence of cancer of several types, with inhaled PAH being assumed to be a main etiological factor (57). For these reasons the previous values for systemic tumors and for tumors due to food uptake are retained, noting that the estimates are very rough and of an order of magnitude that calls for better characterization.

Benzene

Leukemia

Occupational exposure to benzene has been shown to accompany an increased risk primarily of acute myeloic leukemia. Applying the unit risk coefficient of the EPA (15), 8×10^{-6} $(\mu g/m^3)^{-1}$, to the calculated average exposure level, 3.6 $\mu g/m^3$, generates a lifetime leukemia risk of 3×10^{-5}, or about five cases annually in Sweden. Earlier risk assessments of benzene have been reviewed by Bailer and Hoel (58).

Reevaluation of data upon which the risk estimates have been based has indicated that the assessed risks might be too high. The exposure assessment has met difficulties, and the linearity of the dose-response relationship for leukemia has been questioned by Lamm et al. (59) and the Health Council of the Netherlands (60). By applying a multiplicative model, the latter arrives at a risk that is about 4 times lower than the EPA estimate (15), but considers that the true risk at ppb concentrations (1 ppb = 3.1 $\mu g/m^3$) may be 100 times lower than that estimated by the EPA in 1984 (which is similar to that of 1990). The evaluation of Brett et al. (61) indicates the leukemia risk to be some three times lower than the one assumed above. Medinsky points out that risk per unit dose may be higher at low levels because of saturation of metabolism at the high doses where effects have been observed (62).

Other Forms of Cancer

The genotoxic effect from benzene has been enigmatic. It has been difficult to produce mutations in in vitro test systems (63, unpublished data from this laboratory), and DNA and hemoglobin adducts have been observed only recently (64,65). One reason for these difficulties may be that genotoxic metabolites are bound predominantly to S9 proteins in the test medium because of high reactivity, as seen when radiolabeled benzene is used (unpublished data). An important contribution to the solution of the problem is the systematic genotoxicity testing of various benzene metabolites carried out by Glatt et al. (66). In Salmonella typhimurium strain TA1535 only trans-1,2-dihydrodiol and the diol-epoxides proved mutagenic. A surprising effect was the strong mutagenic response to quinone and hydroquinone (and to compounds that can give rise to quinones to a lesser extent) in tests for induction of 6-thioguanine resistance in V79 cells (66). These compounds, in contrast to the alkylating diol-epoxides, were inactive for the

induction of ouabaine resistance (i.e., point mutation). They may act by a mechanism related to the chromosome fragmentation (67,68) to be caused by a range of compounds that can be oxidized to o- or p-quinones which could lead to deletions. Hydroquinone and other benzene metabolites also have been shown to cause genotoxic effects in vivo (69,70).

Cancer tests in the last few years have shown increased incidence of cancer in numerous organs (71–73), which is in accordance with the test substance giving an initiator dose in the entire body. In humans an increased incidence of lymphoma has been shown (74), and in a comprehensive Chinese cohort study, a raised incidence of tumors at several sites, including lung, liver, and colon, was shown (75). In view of this it is reasonable to presume that the total cancer risk is at least three times higher than the leukemia risk. (In the cited Chinese study this ratio was about 10 in males.)

Carbonyl Compounds

Though also formed in larger amounts by the use of methanol or ethanol as engine fuel, quantitatively important air pollutants are low molecular weight aldehydes such as formaldehyde and acetaldehyde, generally formed during combustion of organic matter. Also formed from methanol and ethanol fuels, α,β-unsaturated carbonyl compounds are distinguished for having very high cell toxicity. Double bond epoxidation may lead to more efficiently mutagenic compounds. Because of the carbonyl group's reactivity, these epoxides are cross-linking and, therefore, highly genotoxic.

Formaldehyde

The lifetime cancer risk estimated by applying the EPA unit risk factor, 1×10^{-5} per $\mu g/m^3$, to the average exposure level in Sweden, 1.2 $\mu g/m^3$, would be 1.2×10^{-5}, corresponding to two cases of naso-pharyngeal cancer annually.

Formaldehyde is clearly genotoxic in a large number of test systems (76,77). It has been shown to react with DNA in different ways, with base changes as well as cross-linkages between DNA and proteins as a consequence (78). Formaldehyde can also act as a co-mutagen (cocarcinogen) by obstructing repair of DNA damage (79). From such data one can expect that formaldehyde acts as an initiator in many organs. One complication in risk assessment is that the substance is a normal metabolite, although it may be assumed through compartmentalization to be held separate from the cells' DNA. It should

also be realized that relatively high indoor concentrations of carbonyl compounds, particularly formaldehyde, are created by emission from building materials and the like.

Cancer tests with rodents exposed to formaldehyde in the air show tumors limited exclusively to the nasal membranes (80,81). The dose-response relationship for this effect is markedly convex, a possible consequence of irritation or cell damage leading to promoter action. From only these animal data, it is impossible to determine whether a zero-effect threshold exists or not.

The rat and the mouse breathe only through the nose, unlike to humans. If animal experiments have any relevance to human risk, it would seem possible that formaldehyde exposure could lead to risk of cancer in the nose, pharynx, larynx, and lungs. Epidemiological investigations have been negative for the most part and have led to the assessment (concerning naso-pharynx cancer) that humans are less sensitive to formaldehyde than rats (82). A large study published by the National Cancer Institute (NCI) (83) also produced negative results, but it suggested a synergism between formaldehyde and particles. This study has been criticized (84). Analyzing the Swedish Cancer-Environment Registry and using total cancer incidence to allow for the healthy-worker effect, Ehrenberg et al. (85) found a weakly significant ($p<0.05$), approximately 30% increase of nose and larynx cancer incidence in occupational groups with exposure to formaldehyde (in all approximately 10,000 persons were examined during 1961–1967).

A reevaluation of the above-mentioned NCI study with regard to "the healthy-worker effect" neglected in the original study shows a significant increase of lung cancer risk as well as the total cancer risk (86). With an exposure dose of 1 ppm per year, the relative risk is measured at approximately 1.7 for lung cancer and approximately 1.5 for all cancer forms. Assuming linear dose-risk relationships and applying these figures to the estimated average exposure level, 1.2 ppb, the annual number of lung cancer cases (3000), and total cancer cases (40,000), the following numbers of cases in Sweden are obtained:

lung cancer is:

$1.2 \times 10^{-3} \times 0.7 \times 3\,000 \approx 3$ cases/year

and all cancers are:

$1.2 \times 10^{-3} \times 0.5 \times 40,000 \approx 25$ cases/year.

For several reasons, the risk estimated by application of the unit risk factor based on animal experiments should be considered very uncertain and might very well overestimate the risk of naso-pharynx cancer (87). We find it appropriate to use a figure for all cancer, despite all uncertainties, of about 25 cases annually in Sweden. Either choice might be used for regulatory purposes, if it is realized that further work is required to determine a value of the true risk. In such work, improved understanding of the mechanism of action and, if possible, in vivo dosimetry will play an important role (88,89).

Acetaldehyde

Acetaldehyde is apparently genotoxic among other things, due to its cross-linking ability. According to animal experiments (90), acetaldehyde is cancer-producing in the upper airways, with both initiator and promoter activity. The lifetime cancer risk estimated by applying the unit risk factor, 2×10^{-6}, to the average exposure level in Sweden, approximately 1 µg/m^3, would be 2×10^{-6}, corresponding to 0.2 cases annually in Sweden. This figure is very uncertain but can be taken to indicate that at present exposure levels (which might change with the introduction of ethanol-based fuels) the risk is small.

Alkenes

Ethene

In the judgment of IARC ethene is referred to group 3, meaning that "the agent is not classifiable as to its carcinogenicity to humans" (56). The background of this categorization is an interesting epistemological question. Ethene has been shown beyond doubt to be metabolized in animals (45,91–93) and in humans (20,94–96) to an established animal and probable human carcinogen, ethylene oxide. However, the metabolism is saturable, and the highest concentration of ethylene oxide that can be reached in the tissues corresponds to the one established during exposure to approximately 5 ppm ethylene oxide. In long-term animal tests, a concentration between 10 and 30 ppm is required for obtaining sufficient power to detect the raised incidence at, for instance, 5% significance level in a group of 100 animals (97).

The weighted average concentration to which the Swedish population is exposed is set at 1.8 µg/m^3 (Table 1). Counting with 5% of the inhaled amount being metabolized to ethylene oxide (94,98), the lifetime cancer risk estimated by applying the unit risk factor for ethylene oxide, 1×10^{-4} per µg/m^3, to the average exposure level of

ethene in Sweden would be 1.4×10^{-5}, corresponding to two cases annually.

The absorbed amount corresponds to $(0.05 \times 20 \text{ m}^3/\text{day}) \times (1.8 \times 1010^{-3} \text{ mg/m}^3) \times 365 \text{ (day/year)} = 0.657 \text{ mg/year}$ being metabolized annually, with an annual ethylene oxide dose of

$$\frac{0.657 \text{ mg/year}}{70(\text{kg bw}) \times 28(\text{mg/mmole}) \times 3(\text{h}^{-1})} =$$

$$1.12 \times 10^{-4} \text{ mMh/year} \qquad [7]$$

where 3 h^{-1} is the adopted rate of elimination of ethylene oxide in humans. Using the rad-equivalence for acute doses of 80 rad-equivalents per mMh, the annual rad-equivalent dose is estimated to 9×10^{-3} rad-equivalents per year. Considering that the risk may be about four times lower at low dose rate (8,94), the risk would be 125×10^{-6} in a lifetime or 1.8×10^{-6} per year. In the Swedish population this would correspond to 15 deaths annually. The number of diagnosed cases in Sweden would be about two times larger, or about 30 cases annually. This estimate is higher than the one based on the unit risk factor of EPA by about one order of magnitude. However, it shows certain agreement with observed incidence of leukemias and cancer in blood and lymphatic organs in work environments considering that the incidence of leukemias amounts to about one-tenth of the total cancer incidence. The absence of epidemiological data for other cancers may be due to the short observation periods.

In densely populated and trafficked areas the risk of cancer death may be on the order of 2×10^{-5}/year due to higher concentration of ethene. It must be stressed that the given estimate for ethene has a great uncertainty, due to other uncertainties with respect to average exposure concentration, fraction of inhaled amount that is metabolized to ethylene oxide, and the true value of the rad-equivalent at current dose rates. In addition there is considerable theoretical uncertainty regarding the extrapolation models used. The overall uncertainty has been judged to amount to at least a factor of three (96).

Propene

The weighted average concentration to which the Swedish population is exposed to propene is estimated to 2.3 µg/m^3 (Table 1). As with ethene, it is estimated from animal experiments that approximately 5% of inhaled propene is metabolized to propylene oxide (99). This compound appears to be detoxified 4 times faster than

ethylene oxide in animals exposed to engine exhausts (*45*) to 20 times faster than ethylene oxide in smokers (*98*). The two epoxides are equally effective point mutagens, though ethylene oxide is more effective than propylene oxide with respect to genetic effects involving recombination (*100*). In this situation, it appears prudent to assume the risk from propylene oxide to be five times less than the risk from ethylene oxide. With the rad-equivalence approach we would expect a lifetime risk of 2×10^{-5}, corresponding to some five cases annually.

Butadiene

The lifetime cancer risk estimated by applying the unit risk factor, 3×10^{-4}, to the average ambient level in Sweden, 0.7 $\mu g/m^3$, would be 2.1×10^{-4}, corresponding to 25 cases annually. As judged from animal assays butadiene exhibits a considerably higher risk than ethene (more than one order of magnitude) at equal exposure doses or equal amounts retained in the body. This difference becomes even larger if, as expected from preliminary measurements (unpublished material), the primary metabolite vinyloxirane is detoxified faster than ethylene oxide. From available data (including a cancer test), it is expected that ethylene oxide and vinyloxirane are approximately equally effective mutagens or cancer initiators, and the high potency of butadiene is probably due to the further metabolism of vinyloxirane to diepoxybutane(s) (three isomers possible). *R*- or *S*-Diepoxybutane exhibit a genotoxic potency in several materials that is one to two orders of magnitude greater than that of monofunctional epoxides, an effect attrib-

uted to the ability of the diepoxide to cross-link DNA bases (primarily guanines) in the same DNA strand or in the complementary strands (*101*). This higher potency of diepoxybutane also is compatible with results of cancer tests. Aldehydes such as 2-butenedial also may contribute to bone marrow damage in the same manner as muconaldehyde (*102,103*). Dahl et al. (*104,105*) have demonstrated species differences in metabolism of reactive compounds, the blood concentration of toxic metabolites and of hemoglobin adducts being lower in monkeys than in rats or mice. For that reason risk estimation from animal tests should be based on the doses of essential metabolites measured in both animal models and humans. For these reasons criticism of risk estimation of butadiene from experimental data is well-founded, particularly since comparison with epidemiological data indicate that such extrapolation leads to erroneous values (*106*).

Conclusion

The cancer risks estimated by the lifetime unit risk approach and the risks judged to be more realistic are summarized in Table 4. Due to the incompleteness of the list of compounds considered and with regard to the uncertainties of the estimates, it is appropriate not to compute a total risk by summation of the risks for the individual components. Adding to the uncertainty is the fact that outdoor levels have been considered valid for the indoor situation as well. It appears prudent to consider the adopted estimates in Table 4 to be uncertain by a factor of three.

The deviations of adopted risks from the risks estimated by using unit risk factors cannot be taken to reflect an availability of strong

data that prove the incorrectness of the latter. Rather, they are a reflection of ideas about the background of uncertainties and ways to solve the problems. Major causes of these deviations are the presently hypothetical expectations that the risk is a function of the lifetime accumulated dose rather than of the dose per day and that initiators which deliver a dose all over the body will, as with ionizing radiation, cause cancer in most organs. The latter is indicated to be the case in both humans and animals for PAH, formaldehyde, and benzene. For ethene and ethylene oxide, however, the animal test data have still no counterpart indication in epidemiological observations of excess solid tumors; the observed stomach tumors have occurred at a production plant with simultaneous exposure to other chemicals (*20,107*, unpublished material). A reliable risk estimate for urban air pollution cannot be made without integration of data sets for exposed humans, laboratory animals, and cells combined with improved understanding of action mechanisms of relevance at low exposure levels. As expressed by McClellan et al., this

> is a formidable challenge especially for estimating risks at levels likely to be encountered in the general environment. Because of the substantial data that already exists on diesel exhausts, it is an attractive model for further studies (*10*).

It is our belief that measurement of target doses will be essential in the solution of these problems.

The present risks estimated for certain components (e.g., ethene) are lower as compared to earlier estimates (*4,27,94*). This is due mainly to a change in the pollution level, the earlier estimates using figures valid a decade ago, and the present figures considering the cases induced at today's levels.

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